Update on the NanOx biophysical model applied to innovative radiotherapies

Mario Alcocer Ávila
m.alcocer-avila@ip2i.in2p3.fr

Institut de Physique des 2 Infinis de Lyon (IP2I)
Université Claude Bernard Lyon 1

CNAO-IN2P3 collaboration meeting

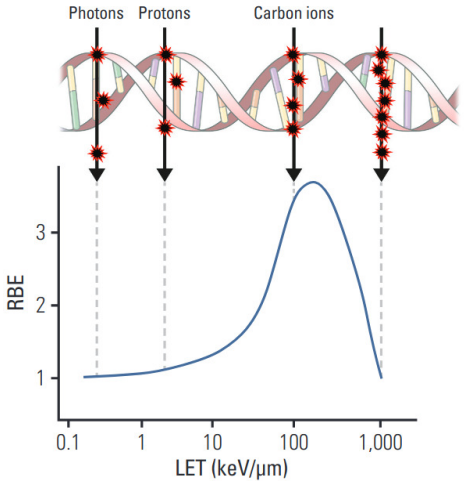
Pavia, March 5, 2026

Outline

1. Need of biophysical models in innovative RTs
2. The NANodosimetry and OXidative stress (NanOx) model
3. NanOx for hadrontherapy
4. NanOx for low-energy ion irradiations
5. Summary of ongoing activities and next steps

Need of biophysical modeling

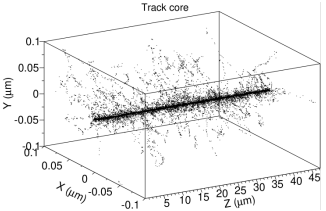
- At a given dose, ions are biologically more effective than photons → Rationale for ion-based innovative RTs (hadrontherapy, TAT, BNCT).
- Because **RBE** depends on many factors, biophysical models are needed to predict it to optimize treatments.
- Only two models: the LEM I and the modified MKM are currently in clinical use.
- Other biophysical models have been developed, including the **NANodosimetry and OXidative stress (NanOx)** model.



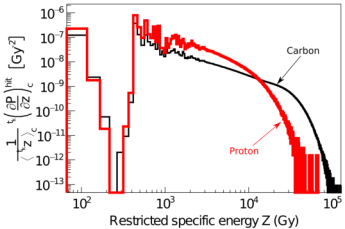
Variation of relative biological effectiveness (RBE) with linear energy transfer (LET) for different radiations (Byun et al. 2021).

The NanOx model

- The NanOx model predicts the cell survival to ionizing radiation.
- It considers:
  - The **stochastic nature** of energy deposition (micrometric and nanometric scales).
  - Sublethal damage and **oxidative stress** induced by free radicals (e.g., $^{\bullet}$OH).
- Cell survival depends on two types of events:
  - Local lethal events (LLE) $\rightarrow$ inactivation of nanometric targets ($\approx$ irreparable DNA damage).
  - Global events (GE)$\rightarrow$ accumulation of sublethal lesions and oxidative stress.



Track of a 2.6 MeV proton in water.



Probability distributions of specific energy in a nanometric target for a 2.6 MeV proton and a 12 MeV/u carbon ion (Alcocer-Ávila et al. 2022).

Main NanOx parameters

- NanOx can be applied to high- and low-energy ion irradiations.
- In both cases the predictions are based on 5 parameters:
  - The geometry of the sensitive volume (SV) (e.g., the radius of the cell nucleus).
  - The quadratic coefficient β_G computed from reference radiation (photons).
  - The 3 parameters of the effective local lethal function (ELLF), used for calculating the survival to local lethal events.

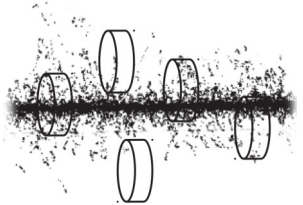
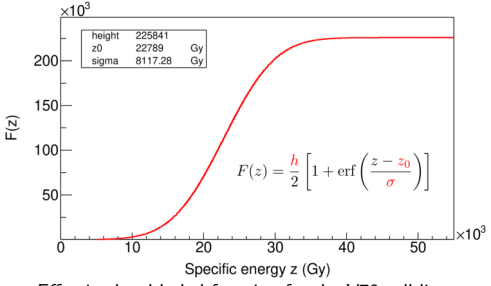


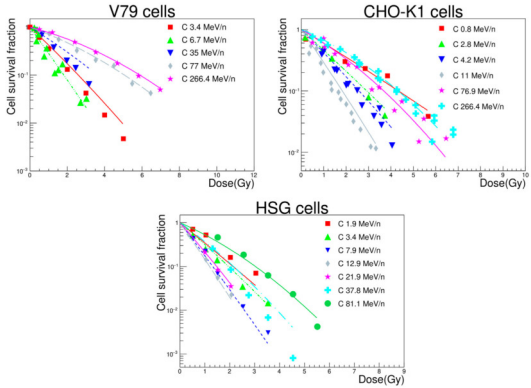
Illustration of cell irradiation in hadrontherapy.



Effective local lethal function for the V79 cell line.

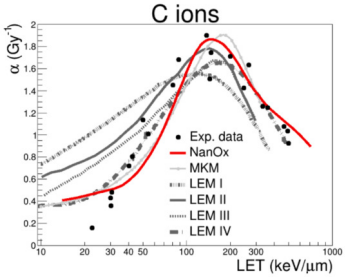
NanOx predictions for hadrontherapy

- The main output of NanOx are the cell surviving fractions as a function of dose.



Survival curves for V79, CHO-K1 and HSG cells irradiated by carbon ions of various energies. NanOx: solid and dashed lines; experimental data (Friedrich et al. 2021): filled symbols (Alcocer-Ávila et al. 2022).

- A LQ fit can be applied to NanOx predictions to construct tables of α and β coefficients for use in TPS.
- A study showed that NanOx predictions are more often more accurate than the ones of other biophysical models.



α values of HSG cells for carbon ions. Experimental data (symbols) is compared to the predictions of several biophysical models (lines) (Monini et al. 2019).

Summary of recent works with NanOx

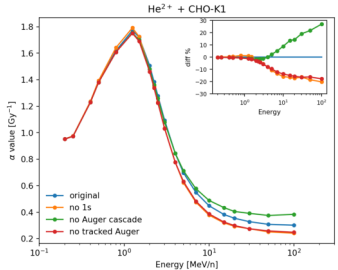
- Application to cell irradiations in a helium SOBP (Berger et al. submitted to phiRO).
- Development of the BioDoseActor in GATE for treatment planning (Ali et al. 2022; Pereda et al. submitted to Medical Physics).
- Extension of the model to low-energy ions (Alcocer-Ávila et al. 2024).
- Analytical expression for computing the β radiobiological coefficient (Alcocer-Ávila et al. 2025).
- First application for computing tumor control probability (TCP) in targeted alpha therapy (TAT) (Levrague et al. 2025).
- Comparison with in vitro data on TAT (Levrague et al. in preparation).
- Investigation of the impact of physical processes on biological response (Strubbia Mangiarelli et al. in preparation).

Studying the impact of physical processes

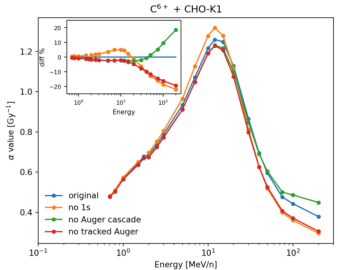
- Influence on biological effect of the core ionization process, using the LPCHEM Monte Carlo code and NanOx.

➠ The results highlight the importance of accurately modeling the physical stage of radiation-matter interactions.

- Ongoing integration of LPCHEM interaction cross sections into Geant4-DNA.



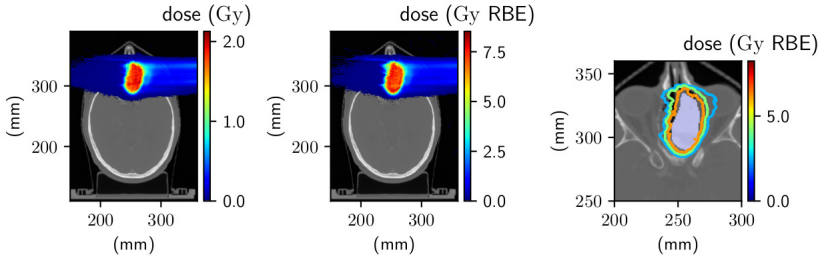
The α coefficient as a function of energy for impact of helium ions on CHO-K1 cells (Strubbia Mangiarelli et al. in preparation).



The α coefficient as a function of energy for impact of carbon ions on CHO-K1 cells (Strubbia Mangiarelli et al. in preparation).

The BioDoseActor for treatment planning

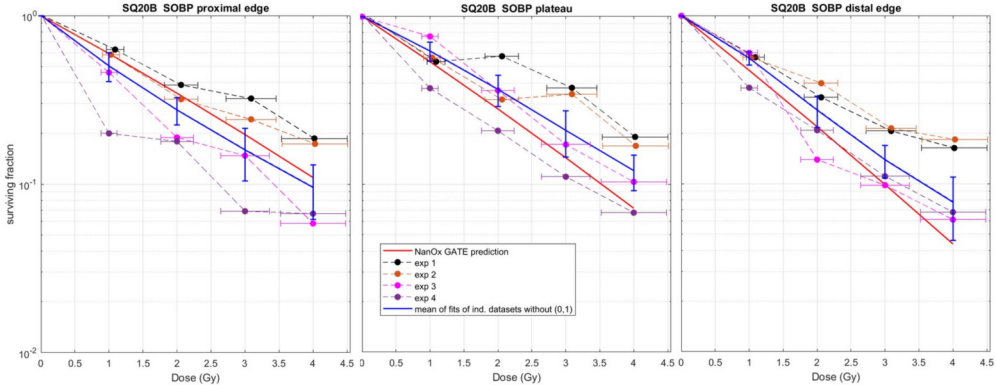
- The **BioDoseActor** was implemented in **GATE** to compute the biological dose for clinical beams in hadrontherapy.
- Biological dose computed at the voxel scale from tables of α and β coefficients provided by NanOx (or other biophysical models).
- First version tested for the Hyogo Ion Beam Medical Center 320 MeV/u C-ion beam line (Ali et al. 2022).
- Recently applied on a PBS C-ion treatment plan for a tumor located in the sinonasal region using the beam line at MedAustron.



Physical and biological PBS C-ion doses simulated with GATE/NanOx for a patient with a tumor in the sinonasal region. (a) physical dose (b) biological dose (c) biological isodose curves 75% (orange), 50% (green) and 30% (blue) of prescription dose (Pereda et al. submitted to Medical Physics).

Cell irradiations in a helium SOBP

- Irradiation of biological samples in the ARRONAX beam line + GATE/BioDoseActor calculations.
- Relatively good agreement between NanOx predictions and experimental measurements.



Irradiation of SQ20B cells in a helium SOBP: comparison of measured cell surviving fractions with the NanOx predictions for three irradiation settings (Berger et al. submitted to phiRO).

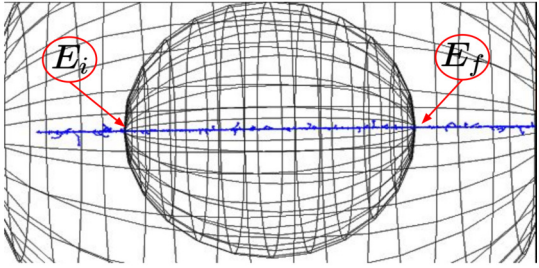
The NanOx model for low-energy ions

- NanOx was adapted for calculations with the low-energy, short-range ions found in TAT and BNCT.

➠ "Track-segment" approximation no longer valid.

Need of considering:

- The energy loss of the ion in the SV.
- The change in the number of lethal events as a function of the ion's energy.
- The impact of cell geometry and the distribution of the therapeutic agent.



Change in ion's kinetic energy when traversing a SV.

$$ {}^{\mathrm{t}_N,t_k}n^* = \int_{{}^{t_k}E_{\mathrm{f}}}^{{}^{t_k}E_{\mathrm{i}}} {}^{\mathrm{t}_N,t_k}\left(\frac{\mathrm{d}n^*}{\mathrm{d}E}\right)\mathrm{d}E = \phi({}^{t_k}E_{\mathrm{i}}) - \phi({}^{t_k}E_{\mathrm{f}}) $$

$$ {}^{t_k}\tilde{Z} = \frac{\eta}{m_{\mathrm{s}}}\left[\psi({}^{t_k}E_{\mathrm{i}}) - \psi({}^{t_k}E_{\mathrm{f}})\right] $$

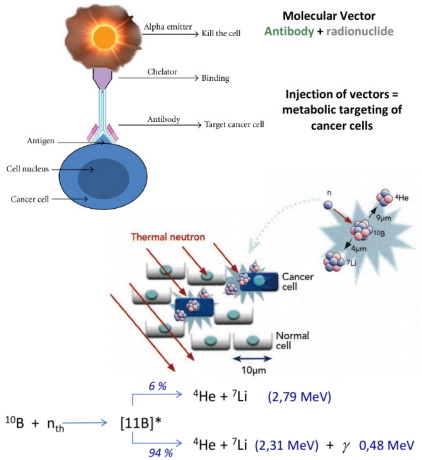
Targeted RTs with low-energy ions

- Targeted Alpha Therapy (TAT).
- Boron Neutron Capture Therapy (BNCT): $^{10}B(n,\alpha)^{7}Li$.

	TAT	BNCT
Isotopes	^{223}Ra, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{211}At...	^{10}B
Ion energies (MeV)	5–9	< 2
Ion ranges (µm)	40–100 (a few cells)	5–9
LET (keV/µm)	60–100	> 150

Common difficulties in biological dose predictions:

- Need of considering dose heterogeneity at the cellular level.
- Relevant SV (nucleus, cytoplasm, membrane? ...).
- Need for specific, multiscale biophysical modeling.

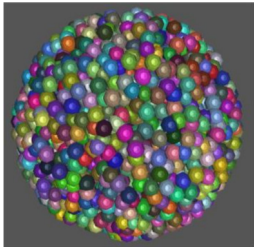


Illustrative scheme of TAT (top) and BNCT (bottom).

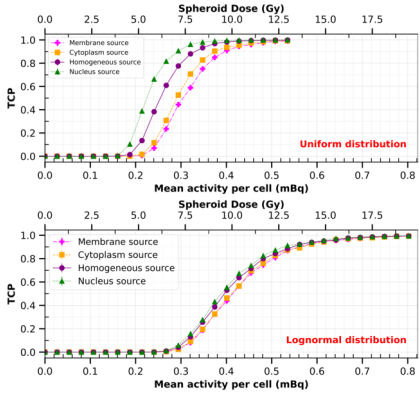
Work on Targeted Alpha Therapy (TAT)

Coupling of **Geant4 + CPOP + NanOx**:

- Geant4 for performing the ion transport.
- CPOP to create multicellular geometry.
- NanOx to compute cell survival and tumor control probability (TCP).



Multicellular geometry simulated in the study with the CPOP code (Maigne et al. 2021).



TCP for 4 intracellular distributions of ^{211}At. Results are for a 95 μm spheroid of HSG cells and 75% compaction (Levrague et al. 2025).

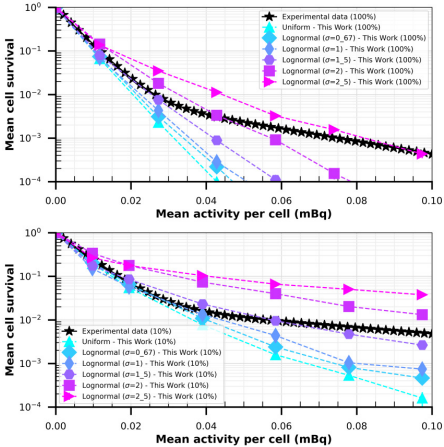
➠ Intracellular distribution of the radionuclide has an impact on TCP at low concentrations.

TAT: A comparison with in vitro data

- NanOx predictions of cell survival were compared with the in vitro experiment of Neti et al. 2007.
- A 100 µm multicellular spheroid was built with CPOP. A fraction of the cells (1%, 10%, 100%) were labeled with Po-210.
- Fair agreement with experimental data for 100% and 10% labeling. Cell death was underestimated for 1% labeling.

➠ Scenarios with a low percentage of labeled cells are difficult to reproduce.

➠ Experimental data obtained under well-controlled conditions is critical for validating biophysical modeling.



Mean cell survival as a function of the activity per cell. The results for a uniform distribution and lognormal distributions with different shape factors are shown for cell labelings of 100% (top) and 10% (bottom) (Levrague et al. in preparation).

Current activities and next steps

Ongoing and upcoming work on targeted RTs:

- Further TAT studies will be performed to improve the NanOx model and validate it with other experimental data sets.
- The application of NanOx to BNCT is underway. It will consider all contributions to the biological dose.
- Progress has been made on the inclusion of an extranuclear SV in NanOx to consider the biological effects of irradiating specific cell compartments.
- The impact on predictions of realistic cell geometries will be assessed in both TAT and BNCT.

Future work on the model will explore:

- The response to high doses and high dose-rates (e.g. applications in FLASH RT).
- Irradiation under hypoxia conditions.
- The indirect effects of ionizing radiation, e.g., bystander and abscopal effects.

Thank you for your attention

Team and collaborations

- PHABIO (IP2I, Lyon): Étienne Testa, Michaël Beuve
- RCM (IP2I, Lyon): Claire Rodriguez-Lafrasse, Gersende Alphonse, Anne-Sophie Wozny
- LIRIS (Lyon): Hamid Ladjal
- LPSC (Grenoble): Rachel Delorme
- LPC (Clermont-Ferrand): Lydia Maigne, Alexis Pereda
- Universidad Nacional de Rosario (Argentina): Mariel E. Galassi, Camila Strubbia

References I

- Alcocer-Ávila, M., É. Testa, and M. Beuve (2025). "Analytical Expression of the β Coefficient of Cell Survival Curves Predicted by the NanOx Model in the Low-Energy Range". In: *Medical Physics* 52.10, e70008. DOI: 10.1002/mp.70008.
- Alcocer-Ávila, M. et al. (2022). "Cell Survival Prediction in Hadrontherapy with the NanOx Biophysical Model". In: *Front Phys* 10, p. 1011063. DOI: 10.3389/fphy.2022.1011063.
- Alcocer-Ávila, M. et al. (2023). "Formalism of the NanOx biophysical model for radiotherapy applications". In: *Front Phys* 11. DOI: 10.3389/fphy.2023.1011062.
- Alcocer-Ávila, M. et al. (2024). "Biophysical Modeling of Low-Energy Ion Irradiations with NanOx". In: *Medical Physics* 51.12, pp. 9358–9371. DOI: 10.1002/mp.17407.
- Ali, Y. et al. (2022). "Estimate of the Biological Dose in Hadrontherapy Using GATE". In: *Cancers* 14.7, p. 1667. DOI: 10.3390/cancers14071667.
- Berger, T. et al. (submitted to phiRO). "Surviving fraction of SQ20B cells in a helium spread out Bragg peak: comparison of experimental data with Monte Carlo predictions based on the NanOx model".
- Byun, H. K. et al. (2021). "Physical and Biological Characteristics of Particle Therapy for Oncologists". In: *Cancer Research and Treatment* 53.3, pp. 611–620. DOI: 10.4143/crt.2021.066.
- Friedrich, T., T. Pfuhl, and M. Scholz (2021). "Update of the particle irradiation data ensemble (PIDE) for cell survival". In: *J Radiat Res* 62.4, pp. 645–655. DOI: 10.1093/jrr/rrab034.
- Gervais, B. et al. (2006). "Numerical simulation of multiple ionization and high LET effects in liquid water radiolysis". In: *Radiat Phys Chem* 75.4, pp. 493–513. DOI: 10.1016/j.radphyschem.2005.09.015.

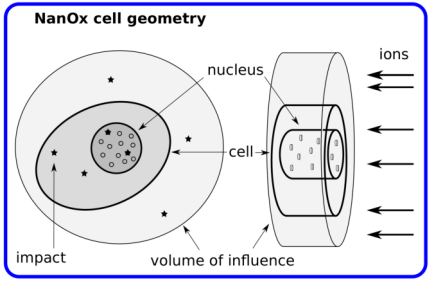
References II

- Levrague, V. et al. (2025). "Impact of Intracellular Radionuclide Distribution in a Monte Carlo Biophysical 3D Multi-Cellular Model for Targeted Alpha Therapy". In: *Medical Physics* 52.7, e17917. DOI: 10.1002/mp.17917.
- Levrague, V. et al. (in preparation). "In silico modeling of non-uniform alpha-emitter distributions in 3D multicellular clusters: comparison with in vitro data".
- Maigne, L. et al. (2021). "CPOP: An open source C++ cell POPulation modeler for radiation biology applications". In: *Physica Medica* 89, pp. 41–50. DOI: 10.1016/j.ejmp.2021.07.016.
- Monini, C., É. Testa, and M. Beuve (2017). "NanOx Predictions of Cell Survival Probabilities for Three Cell Lines". In: *Acta Phys Pol B* 48.10, p. 1653. DOI: 10.5506/APhysPolB.48.1653.
- Monini, C. et al. (2019). "Comparison of Biophysical Models with Experimental Data for Three Cell Lines in Response to Irradiation with Monoenergetic Ions". In: *Phys Imaging Radiat Oncol* 12, pp. 17–21. DOI: 10.1016/j.phro.2019.10.004.
- Monini, C. et al. (2020). "Determination of the Effective Local Lethal Function for the NanOx Model". In: *Radiat Res* 193.4, p. 331. DOI: 10.1667/RR15463.1.
- Neti, P. V. S. V. and R. W. Howell (2007). "Biological Response to Nonuniform Distributions of ^{210}Po in Multicellular Clusters". In: *Radiation Research* 168.3, pp. 332–340. DOI: 10/c8gnbv.
- Pereda, A. et al. (submitted to Medical Physics). "Calculating biological dose distributions in hadrontherapy using GATE: the BioDose actor".
- Strubbia Mangiarelli, C. et al. (in preparation). "Influence of core ionization processes on cell survival calculated with the NanOx biophysical model".

BACKUP SLIDES

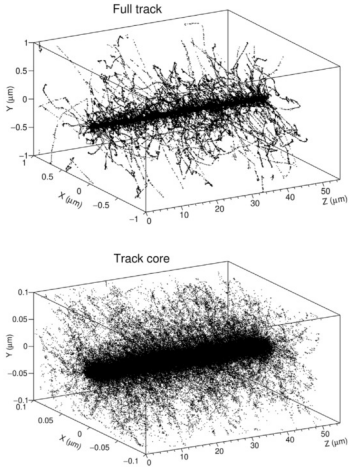
Basic assumptions for hadrontherapy

- One SV: the cell nucleus.
- SV with cylindrical geometry and ion beam parallel to the SV axis.
- Irradiation in **“track-segment” conditions**.



Cell geometry used in NanOx calculations for hadrontherapy (Alcocer-Ávila et al. 2022).

- Presence in ion tracks of a **“core”** and a **“penumbra”**.



A carbon ion track of 12 MeV/n and a zoom on its core.

Cell survival calculation in hadrontherapy

- The average cell surviving fraction is computed as:

$$\overline{S(D)} = \sum_{K=0}^{\infty} P(K, D) \cdot \langle {}^{c_K}S \rangle_{c_K}$$

$P(K, D)$: probability of K impacts at dose D;
$\langle {}^{c_K}S \rangle_{c_K}$: mean survival over all configurations.

- The surviving fraction includes the contribution of local and global lethal events, considered as independent:

$${}^{c_K}S = {}^{c_K}S_{LLE} \times {}^{c_K}S_{GE}$$

- NanOx has been applied for computing surviving fractions of several cell lines (e.g. HSG, CHO-K1, V79, SQ20B) irradiated by photons and different ions (Monini et al. 2017).

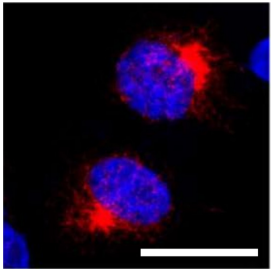


Image of HSG cells (Kim et al. 2019).

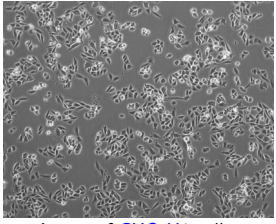


Image of CHO-K1 cells.

Cell survival to local lethal events

- The modeling of LLE is based on the inactivation of a single local target among N distributed uniformly in the SV.
- Local targets modeled as cylinders with diameter $d_\mathrm{t} = 20$ nm and length $L_\mathrm{t} = 10$ nm
- NanOx calculations are based on the **effective number of local lethal events (ENLLE)**:

$$ {}^{\mathrm{c}_i,\mathrm{c}_k}n^* = -\ln\left(1 - {}^{\mathrm{c}_i}f({}^{\mathrm{c}_i,\mathrm{c}_k}z)\right) $$

${}^{\mathrm{c}_i}f({}^{\mathrm{c}_i,\mathrm{c}_k}z)$: probability that target i is inactivated after an impact with configuration c_k inducing the **restricted specific energy** ${}^{\mathrm{c}_i,\mathrm{c}_k}z$ in i

- The cell surviving fraction to LLE for a configuration c_K of radiation impacts can be expressed in terms of an **effective local lethal function (ELLF)** $F(z)$:

$$ {}^{\mathrm{c}_K}S_\mathrm{L} = \prod_{k=1}^{K} \exp\left(-F\left({}^{\mathrm{c}_k}z\right)\right) $$

with:

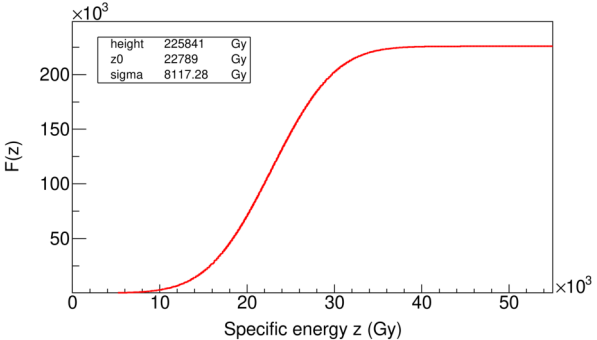
$$ F(z) = -N\ln\left(1 - f\left(z\right)\right) $$

The effective local lethal function (ELLF)

- The ELLF characterizes the response of each cell line by means of 3 free parameters (z_0, σ, h) determined through a fit to experimental values of α (Monini et al. 2020).

$$F(z) = \frac{h}{2}\left[1 + \mathrm{erf}\left(\frac{z - z_0}{\sigma}\right)\right]$$

z_0: threshold of the function
σ: extent of the increase
h: height of the response



Effective local lethal function for the V79 cell line.

Cell survival to global events

- The computation of the cell survival to GE uses the notion of **chemical specific energy,** $\tilde{Z}$:

$$ {}^{c_K}\tilde{Z} = {}^{c_K}\mathrm{RCE} \cdot {}^{c_K}Z $$

  ${}^{c_K}\mathrm{RCE}$ is the **relative chemical effectiveness**, defined as the ratio of the **chemical yield** (i.e., number of reactive chemical species generated per 100 eV) of the ion, ${}^{c_K}G$, to that of reference radiation, G_r:

$$ {}^{c_K}\mathrm{RCE} = \frac{{}^{c_K}G}{G_\mathrm{r}} $$

- These quantities are obtained from MC simulations with the LPCHEM code (Gervais et al. 2006).

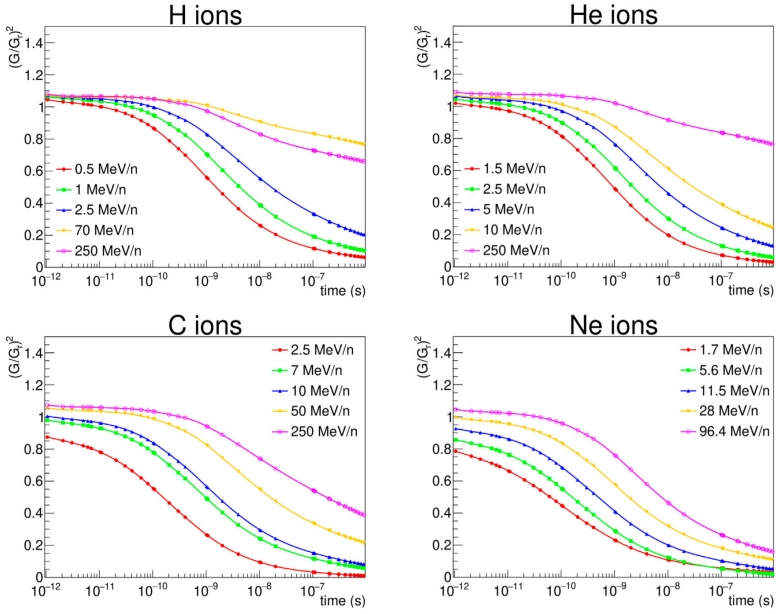
- Currently only primary $^\bullet\mathrm{OH}$ are considered for cell survival calculation.

- The cell surviving fraction to GE for a configuration c_K of radiation impacts is then:

$$ {}^{c_K}S_\mathrm{G} = \exp\left(-\alpha_\mathrm{G}\,{}^{c_K}\tilde{Z} - \beta_\mathrm{G}\,{}^{c_K}\tilde{Z}^2\right) $$

- α_G and β_G are determined for each cell line from cell survival curves for reference radiation.

- We currently set $\alpha_\mathrm{G} = 0\ \mathrm{Gy}^{-1}$ to perform an independent adjustment of local and global events.

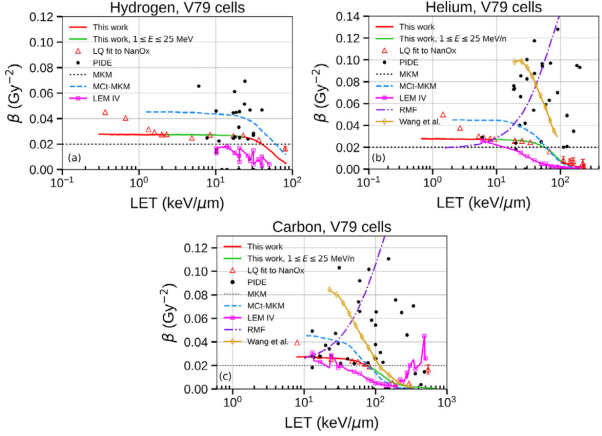


RCE^2 as a function of time for hydrogen, helium, carbon and neon ions of different energies (Alcocer-Ávila et al. 2023).

Analytical calculation of the β coefficient

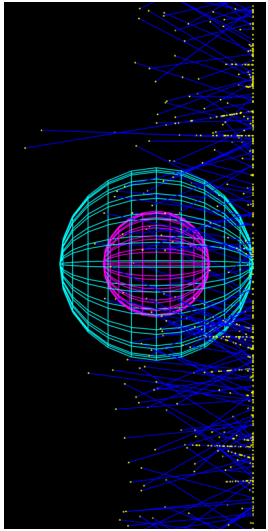
- Computing the β coefficient of cell survival curves is time-consuming.
- Experimental data show a large scatter.
- Biophysical models lead to different predictions.
- An analytical expression was derived from NanOx for energies below 25 MeV/n.

$$\beta \approx \beta_{\mathrm{r}}\,(\mathrm{RCE})^2 \left[1 - \frac{\alpha \cdot a \cdot \mathrm{LET}}{\sigma_0}\right]^2 \cdot \frac{\left(1 + \frac{m_1}{2}\right)}{(1 - m_1)^2}$$

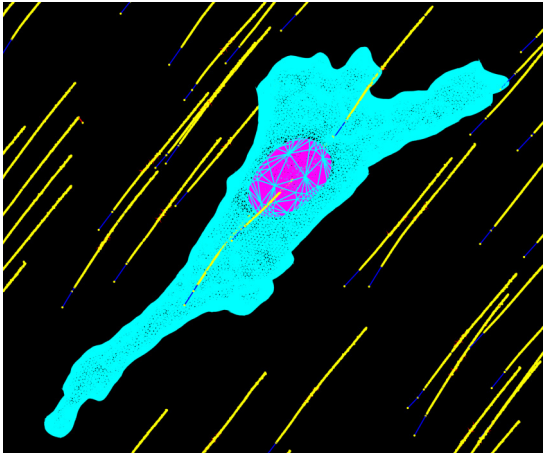


β as a function of LET for impact of hydrogen, helium and carbon ions on V79 cells (Alcocer-Ávila et al. 2025).

Examples of cell geometries



A simple spherical cell model in Geant4.



Irradiation of a realistic glioblastoma cell (U87) in Geant4.

Overview of NanOx for low-energy ions

For low-energy ions, the number of LLE and GE will vary as a function of the ion's energy across the SV. Main hypothesis are:

1. Narrow tracks.
2. Negligible fluctuations from one radiation configuration to another (average over a large number of particles of the same type T_k and energy E_k).

- The cell survival to LLE and GE can be computed from the effective number of local lethal events and the concentration of primary reactive chemical species, respectively.

- The ENLLE is given by:

$$ {}^{\mathrm{t}_N,t_k}n^* = \int_{{}^{t_k}E_\mathrm{f}}^{{}^{t_k}E_\mathrm{i}} {}^{\mathrm{t}_N,t_k}\left(\frac{\mathrm{d}n^*}{\mathrm{d}E}\right)\mathrm{d}E $$

where ${}^{t_k}E_\mathrm{i}$, ${}^{t_k}E_\mathrm{f}$ denote the energy of the ion at the beginning and end of the track in the SV.

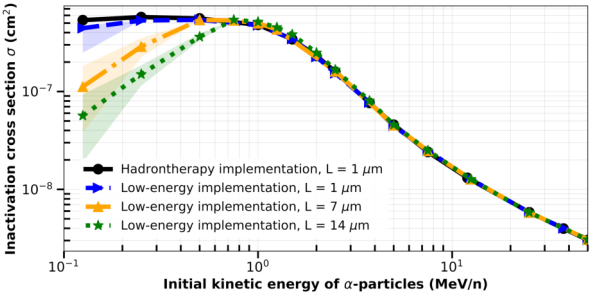
- Similarly, for GE the concentration of primary reactive chemical species is expressed as:

$$ {}^{t_k}Y = \frac{1}{m_\mathrm{s}} \int_{{}^{t_k}E_\mathrm{f}}^{{}^{t_k}E_\mathrm{i}} {}^{t_k}G(E)\mathrm{d}E $$

with m_s the mass of the SV.

Consistency and relevance at low energies

- A recent study showed that NanOx offers a **consistent framework** for all ion-based RTs.
- The NanOx versions for hadrontherapy and low-energy ions were compared and agreed for $E \gtrsim 1$ MeV/n.
- For $E \lesssim 1$ MeV/n, the low-energy version showed an effect on the investigated biogical output (i.e. cell inactivation cross section).
- The **influence of target geometry** also became noticeable at low energies.



Inactivation cross section as a function of the initial kinetic energy of α-particles (Alcocer-Ávila et al. 2024).